UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,937	02/15/2002	Herbert M. Dean	dcan0202con	3941

23580 7590 07/28/2004

MESMER & DELEAULT, PLLC
41 BROOK STREET
MANCHESTER, NH 03104

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,937	DEAN ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3/30/2004.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed March 30, 2004 have been entered.

Claims 1-18 are pending. Claims 11-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 3.

Claim 18 is not allowable as recited because of the amendment filed June 20, 2003 has broadened the scope of the claim. The reason for allowance is clear as set forth in the office action mailed January 29, 2003 that claim 18 (pre-June 20, 2003 amendment) is allowed because of no excipient recited in the claim then. The scope of claim 18 has changed according the amendments filed June 20, 2003 to include other ingredients and therefore, it should be rejected under the same ground as claims 1-10 and 17. Examiner apologizes the oversight.

Warning

Applicant is advised that should claim 1 be found allowable, claim 17 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Both claims are drawn to composition comprising the same components.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearle (American Heart Journal, 1990 Sep; 120(3):739-742), Carruthers et al. (American Journal of Cardiology, 1993;71:575-581), Abby et al. (Journal of the American Board of Family Practice, 1998; 11(5):391-398), Oakley et al. (The Journal of Nutrition, 1996;126(3): 751S – 755S), and Behounek et al. (US Patent 5,691,375) in view of Rork et al. (US Patent 5,882,682), references of record.

Pearle teaches that beta-blockers such as timolol, metoprolol, atenolol, and propranolol reducing the overall mortality and the incidence of recurrent myocardial infarction (See the abstract; also page 740, col. 1, second paragraph).

Carruthers et al. teaches atenolol reducing the risk of coronary heart disease (See the abstract).

Abby et al. teaches folic acid and vitamin B_6 are useful in reducing the risk of coronary heart disease such nonfatal myocardial infarction and fatal coronary heart disease (See particularly page 395, Table 2).

Oakley et al. teaches vitamin B_{12} supplement is useful with folic acid administration to avoid the folic acid adverse effect: B_{12} deficiency (See page 3, third and fourth paragraph).

Behounek et al. teaches HMG-CoA reductase inhibitor such as pravastatin is useful in reduce the risk of cardiovascular event (See the abstract).

The references do not expressly the incorporation of beta-blockers such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B_6, and vitamin B_{12} into a single once-a-day dosage unit.

Rork et al. teaches a sustained release system that can include beta-bloackers such as timolol, metoprolol, atenolol, and propranolol and statin cholesterol lowering agents such as simvastatin, pravastatin, and lovastatin (See col. 6, line 64-66 and col. 7, line 16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B_6, and vitamin B_{12} into a single once-a-day dosage unit.

One of ordinary skill in the art would have been motivated to incorporate beta-blockers, such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors, such as pravastatin, folic acid, vitamin B_6, and vitamin B_{12} into a single once-a-day dosage unit. All the agents herein: different beta-blockers such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, and vitamin B_6 are all known to reduce risk of cardiovascular diseases. Possessing the teachings of the cited prior art, combining two or more agents which are known to be useful to reduce risk of cardiovascular disease individually into a single sustained release, once-daily composition useful for the very same purpose is prima facie obvious (See *In re Kerkhoven* 205 USPQ 1069), absent evidence to the contrary. Furthermore, possessing the teaching of Oakley et al., one of ordinary skill in the art would incorporate vitamin B_{12} into any folic acid containing composition including the instant composition since vitamin B_{12} administration would prevent folic acid adverse effect such as vitamin B_{12} deficiency.

Response to Arguments

Applicant's arguments filed March 30, 2004 averring the basis of combining the herein claimed actives relying on Rork have been considered, but are not found persuasive. The motivation to combine the herein claimed active compounds is provided by the cited prior art because all the agents herein: different beta-blockers such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, and vitamin B_6 are all known to reduce risk of

cardiovascular diseases. Possessing the teachings of the cited prior art, combining two or more agents which are known to be useful to reduce risk of cardiovascular disease individually into a single sustained release, once-daily composition useful for the very same purpose is prima facie obvious (See *In re Kerkhoven* 205 USPQ 1069), absent evidence to the contrary. Furthermore, possessing the teaching of Oakley et al., one of ordinary skill in the art would incorporate vitamin B_{12} into any folic acid containing composition including the instant composition since vitamin B_{12} administration would prevent folic acid adverse effect such as vitamin B_{12} deficiency.

Applicant's arguments filed March 30, 2004 averring the examiner inappropriately applying *In re Kerkhoven* have been considered, but are not found persuasive. Please note that although beta-blocker and statins have different kind of mechanism of action, and yet, they are useful for cardioprotection individually (i.e., reducing the risk of cardiovascular disease). Therefore, combining them together into a single composition useful for the very same purpose is obvious. Applicant also apparently confused with mechanism of action with therapeutic goal in page 3 last paragraph bridging to page 4, first paragraph. Statins and beta-blockers are well-known to have different mode of action or mechanism of action. However, as taught in the cited prior arts, they are useful for reducing the risk of cardiovascular disease individually. Therefore, combining them together in a composition for the very same purpose is obvious. As the matter of fact, in the pharmaceutical art, there are so many examples that two drugs having different mechanism of action but for the same purpose as concomitantly employed together; to name a few: asthma treatment: corticosteroids and beta-2 agonists

together; allergy medicine: combining anti-histamine and nasal decongestant; antihypertension medicine: calcium channel blocker plus ACE inhibitor together, angiotensin-2 inhibitor and diuretic together; anti-diabetic: metformin plus troglitazone and/or insulin; anti-cancer: almost always using multi-drug treatment; anti-infective: Sulfamethoxazole and trimethoprim (Bactrim DS); GI: antacid plus H2-inhibitors.; and erectile dysfunction treatment: Papaverine, Phentolamine, and PGE1 together (Trimix). The examples listed above are drugs that are having a very different mechanism of action and yet being combined for the very same therapeutic goal.

Applicant's arguments filed March 30, 2004 averring the Examiner mischaracterized Dr. Gurwitz's declaration have been considered, but are not found persuasive. Examiner notes that Dr. Gurwitz's declaration merely points out that the combination is novel (see paragraph 10). Furthermore, Dr. Gurwitz's declaration merely expresses his own opinion towards the instant subject matter. With all due respect, Dr. Gurwitz's own opinion is not the standard for patentability of the instant subject matter. The declaration does not provide any factual evidence to rebut Examiner's position that the instant components are useful for cardioprotection individually, and combining them together in a single composition useful for the very same purpose is obvious (See *In re Kerkhoven* supra). Moreover, the arguments with regard to improving compliance in elderly patients are not convincing. The declaration apparently includes statements which amount to an affirmation that the claimed subject matter functions as it was intended to function (to solve compliance problem in the elderly patient population).

This is not relevant to the issue of nonobviousness of the claimed subject matter and provides no objective evidence thereof. See MPEP § 716.

Applicant's arguments in page 6-7 of the response filed March 30, 2004 averring the Office as wrong to ask for evidence of improving compliance because the Office is "confusing" utility with obviousness have been considered, but are not found persuasive. Examiner's remarks with regard to "no evidence of improving compliance is provided" were directed to "unexpected benefit". Applicant apparently misunderstood the Examiner's position. Since no objective evidence to evaluate whether unexpected benefits is present or not, the claims are considered properly rejected under 35 USC 103(a).

Furthermore, Applicant's arguments filed March 30, 2004 averring the cited prior art's failure to teach the applicant's motivation for combining the herein claimed ingredients (beta-blockers, statins, and other active ingredients), i.e., to improve compliance in elderly patients, have been fully considered but they are not persuasive. Examiner notes that such motivation has never been recited in the claims. Arguments drawn to the unclaimed limitation is considered moot. Even if such limitation is recited in the claims, the intended use does not lend patentable weight in claims that are drawn to composition.

Applicant's arguments in page 6-7 of the response filed March 30, 2004 averring the only solution to solve patient's compliance as physician-patient education have been considered, but are not found persuasive. The arguments are not seen to be relevant to the instant claims. Examiner notes that the instant claims are directed to composition,

not a method of improving elderly patient's compliance to their medication. Agains, as discussed above, the motivation to combine is provided by the cited prior arts: All of the herein claimed agents: different beta-blockers such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, and vitamin B_6 are all known to reduce risk of cardiovascular diseases individually. Possessing the teachings of the cited prior art, combining two or more agents which are known to be useful to reduce risk of cardiovascular disease individually into a single sustained release, once-daily composition useful for the very same purpose is prima facie obvious (See *In re Kerkhoven* 205 USPQ 1069), absent evidence to the contrary. Furthermore, possessing the teaching of Oakley et al., one of ordinary skill in the art would incorporate vitamin B_{12} into any folic acid containing composition including the instant composition since vitamin B_{12} administration would prevent folic acid adverse effect such as vitamin B_{12} deficiency.

Applicant's arguments in page 7, last paragraph bridging page 8, first paragraph in response filed March 30, 2004 averring Rork as providing motivation to combine have been considered, but are not found persuasive. As discussed above, the motivation to combine is provided in the primary references. Rork is cited to show that sustained release formulation is well-known in the art that can be used to combine various agents together into one product.

Applicant's arguments filed March 30, 2004 with regard to hindsight arguments have been considered, but are not found persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper

hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As discussed above, the motivation to combine is clearly provided in the cited prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Patent Examiner
Art Unit 1617